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EXAMINER	
ANDERSON, JAMES D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,840	SOON-SHIONG ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-104,106-123 and 125-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-104,106-123 and 125-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 12/1/2008 and 5/26/2009, are acknowledged and entered. Claims 105 and 124 have been cancelled by Applicant. Claims 75-104, 106-123, and 125-129 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 105 and 124 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments have been fully and carefully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Upon further consideration, new grounds of rejection are being applied against the pending claims. Accordingly, this Office Action is Non-Final.

Priority

No support is found in prior-filed U.S. Provisional Application No. 60/130,863, filed 4/22/1999, for the limitation "...wherein the conventional dose of paclitaxel is 135-175 mg/m^2 over a period of three weeks" as recited in claims 90-104, 106-123, and 125-129. At page 6, lines 12-14, the '863 application discloses conventional treatment with paclitaxel at a dose of 200-250 mg/m^2 every 3 weeks.

Accordingly, claims 90-104, 106-123, and 125-129 are not afforded priority to the '863 application, and therefore have a priority date of **4/21/2000**, the filing date of PCT/US00/10849.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 12/1/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90-104, 106-123, and 125-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amount and timing of administration of paclitaxel recited in the instant claims is confusing. Independent claim 90 recites administering paclitaxel to a subject "over a period of 7 days or more", wherein the amount of paclitaxel is 1% to 20% of a conventional dose of paclitaxel "over the same period", wherein the conventional dose of paclitaxel is 135-175 mg/m^2 "over a period of three weeks".

As a first matter, the metes and bounds of the limitation "over a period of 7 days or more" is unclear. It is not clear whether this means continuous administration over 7 days or more (*e.g.*, daily administration for 7 days or more) or whether this means, for example, a single administration on Day 1 and then subsequent administrations on Days 8, 16, 24, etc. Alternatively, the claims could be interpreted to mean administration on Day 1 and then a second administration a year later. Such would appear to meet the limitation "administering paclitaxel to a subject over a period of 7 days or more".

Secondly, the limitation "wherein the amount of paclitaxel is 1% to 20% of a conventional dose of paclitaxel *over the same period*" is confusing when taken together with the limitation, "wherein the conventional dose of paclitaxel is 135-175 mg/m^2 *over a period of three weeks*". Is the administration of paclitaxel "over the same period" in reference to over a period or 7 days or more or in reference to over a period of three weeks"? For example, 1% to 20% of

135-175 mg/m^2 is a range of 1.35-35 mg/m^2 over a period of 3 weeks. However, this range is only 0.45-11.67 mg/m^2 over a period of 7 days.

It is not clear what doses of paclitaxel are intended to be administered by the claimed method. While 1% to 20% of 135-175 mg/m^2 is easy readily calculated, over what period of time the 1% to 20% is intended to be administered is not clear from the language of the claims.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-89 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method of administering paclitaxel comprising administering paclitaxel to a subject "wherein the plasma level of paclitaxel in the subject is maintained at 0.01 -0.05 μg/mL over a period of 7 days or more".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to an administration method requiring administration of paclitaxel to a subject in a certain dose range, by a certain administration route, and in a certain administration

interval so as to maintain a plasma level of paclitaxel in the subject of 0.01-0.05 μg/mL over a period of 7 days or more.

To provide adequate written description and evidence of possession of claimed subject matter, the specification must provide sufficient distinguishing characteristics of the subject matter.

The specification provides no description of any specific doses, administration routes, or administration regimens that would result in maintenance of the claimed plasma level of paclitaxel over a period of 7 days or more. Other than broad dose ranges (*e.g.*, "about 1% to equal to or about 99%" of the conventionally administered dose), administration routes (*e.g.*, orally, intravenously, locally), and administration intervals (over periods ranging from "about 2 days" to "less than about 365 days"), Applicants provide no description of administration methods that result in maintenance of a plasma level of 0.01-0.05 μg/mL paclitaxel over a period of 7 days or more. It is simply not reasonable to assume that administration of paclitaxel in any dose of about 1% to about 99% of paclitaxel conventionally administered (page 8, lines 11-27), over a period of from about 2 days to less than about 365 days (page 9, lines 11-27), by any administration method, will lead to maintenance of a plasma level of 0.01-0.05 μg/mL paclitaxel over a period of 7 days or more as described by Applicants in the specification. It is noted that Applicants provide no specific examples of any such administration regimens (*e.g.*, administration of 2 mg/m^2 paclitaxel by intravenous infusion for 1 hour every day for 30 days) that result in the plasma level of paclitaxel in the subject being maintained at 0.01-0.05 μg/mL over a period of 7 days or more.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed administration method, which simply recites "administering paclitaxel to a subject" such that "the plasma level of paclitaxel in the subject is maintained at 0.01-0.05 μg/mL over a period of 7 days or more". One of skill in the art would not recognize from the disclosure that the applicant was in possession of such a method because Applicants have provided no description of any such administration methods that actually result in maintenance of the claimed plasma level of paclitaxel over a period of 7

days or more. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Response to Arguments

Applicants traverse the instant rejection, stating that claim 75 provides specific plasma concentrations to be reached in the claimed method of administration. Applicants submit that because pharmacokinetic parameters of paclitaxel are known in the art, one skilled in the art "can calculate an appropriate dose and dosing interval to achieve steady-state concentration of paclitaxel in plasma". This argument is not persuasive because the claims don't merely require achieving a certain concentration of paclitaxel in the blood, but rather require that the plasma level in the blood be "maintained" over a period of 7 days or more. As such, the claims require that the plasma level of paclitaxel in the blood remain, over a period of 7 days or more, in the specific range of 0.01-0.05 μg/mL. If at any time after 7 days during or after the administration of paclitaxel the plasma level is less that 0.01 mg/mL or greater than 0.05 mg/mL, the administration fails to achieve the desired effect. Furthermore, pharmacokinetic parameters of drugs are dependent upon the administration rate, dose, and route of administration. There does not exist a "standard" pharmacokinetic profile for any drug. If the pharmacokinetics of paclitaxel are dependent on administration rate, dose, and route of administration, how is the skilled artisan to "calculate" an appropriate dose and dosing interval to achieve the claimed maintenance of plasma paclitaxel in the range of 0.01 to 0.05 mg/mL over 7 days or more? What “standard” paclitaxel administration regimen is the skilled artisan to use for such a calculation? Applicants have failed to point to any reference that might be used to make such a calculation. For example, Kearns *et al*. (Seminars in Oncology, 1995, vol. 22, no. 3, Suppl. 6, page 16-23) teach that paclitaxel displays nonlinear pharmacokinetics in humans and both peak plasma paclitaxel concentrations and area under the curve of the concentration versus time profile will change disproportionately to changes in dose (Abstract).

As discussed above, Applicant’s description of dosing and dosing intervals to achieve the desired plasma levels of paclitaxel merely suggest that there exists a dose, dosing interval, and

administration route whereby a plasma level of 0.01-0.05 μg/mL paclitaxel might be maintained over a period of 7 days or more. However, at the time the invention was made, Applicants had not determined such doses, dosing intervals, or administration routes. Applicants are imposing the burden of extensive testing upon the skilled artisan to identify administration methods (e.g., doses, intervals of administration, routes of administration, etc.) that may result in the claimed plasma levels of paclitaxel, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to administer paclitaxel that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such a plan, and, therefore, did not have written description of the full scope of the administration method now claimed. Claims and a disclosure that require the public to conduct random hit-or-miss testing to determine whether any particular administration regimen of paclitaxel meets the limitation of maintaining the plasma level of paclitaxel at 0.01-0.05 μg/mL over a period of 7 days or more are evidentiary of lack of written description of the claimed administration method.

Claim Rejections - 35 USC § 103 – New Grounds of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 75-79, 81, 88, 90-96, 98, 106-115, 117, and 125-129 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Broder *et al***. (WO 98/53811; Published December 3, 1998) in view of **Liebmann *et al***. (Br. J. Cancer, 1993, vol. 68, pages 1104-1109).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel to a subject wherein the plasma level of paclitaxel in the subject is maintained at 0.01-0.05 ug/mL over a period of 7 days or more (claim 75) or administering paclitaxel to a subject over a period of 7 days or more, wherein the amount of paclitaxel is 1-20% of a conventional dose of paclitaxel over the same period, and wherein a therapeutically effective plasma level of paclitaxel in the subject is maintained throughout the period of 7 days or more, wherein the conventional dose of paclitaxel is 135-175 mg/m^2 over a period of three weeks (claim 90).[1]

Broder *et al*. disclose administration of taxane antineoplastic agents orally to human patients suffering from taxane-responsive disease conditions and made sufficiently bioavailable to achieve therapeutic blood levels (Abstract). The dosage range of orally administered taxane target agents is disclosed to be in the range of from about 20 mg/m^2 to 1000 mg/m^2 or about 2-30 mg/kg as single or divided (2-3) daily doses, which maintain the plasma levels of paclitaxel in humans in the range of 50-500 ng/mL for extended periods of time (*e.g.*, 8-12 hours) after each oral dose (page 16, line 19 to page 17, line 3). Such plasma levels of paclitaxel are sufficient to provide the desired therapeutic activities of the target drug, *e.g.*, inhibition of tubulin disassembly (which occurs at levels of about 0.1 μM, or about 85 ng/mL) and inhibition of protein isoprenylation (which occurs at levels of 0.03 μM, or about 25 ng/mL) which are directly related to its antitumor effects by inhibiting oncogene functions and other signal-transducing proteins that play a pivotal role in cell growth regulation.

Preferred dosing schedules for administration of oral paclitaxel are (a) the daily administration to a patient in need thereof of 1-3 equally divided doses providing about 20-1000

mg/m^2 (based on body surface area), and preferably about 50-200 mg/m^2, with said daily administration being continued for 1-4 consecutive days each 2-3 weeks, or (b) administration for about one day each week (page 23, lines 4-9). Accordingly, oral administration of one 20 mg/m^2 dose of paclitaxel one day every three weeks meets the limitation of administering 1-20% of a conventional dose of 135-175 mg/m^2 over a period of three weeks.

Broder *et al*. disclose that oral administration of taxanes in accordance with the invention may actually decrease toxic side effects in many cases as compared with currently utilized IV therapy. Rather than producing a sudden and rapid high concentration in blood levels as is usually the case with an IV infusion, absorption of the active agent through the gut wall (promoted by the enhancing agents), provides a more gradual appearance in the blood levels and a stable, steady-state maintenance of those levels at or close to the ideal range for a long period of time (page 23, lines 12-18).

A variety of clinical data have shown that it would be desirable to keep the circulating plasma concentrations within a certain "window" in order to maximize the anti-tumor activity and minimize the side effects, especially neutropenia. For many tumor types, it is believed that low, but long-term, exposure of tumor cells in the body results in better clinical results. Thus, plasma levels of about 0.03 micromolar would be expected to inhibit cancer-cell protein isoprenylation and levels of about 0.1 micromolar would be expected to block disassembly of microtubules. There are clinical data showing that constant intravenous administration over several days to achieve a "window" of about 0.05 to 0.1 micromolar in the circulation can minimize toxicities and cause tumor regressions, sometimes even in patients whose tumors did not respond to 3-hour infusion regimens (page 25, lines 14-23).

Liebmann *et al*. disclose that in human tumor cell lines exposed to paclitaxel *in vitro*, the fraction of surviving cells fell sharply after exposure for 24 hours to paclitaxel concentrations ranging from 2 to 20 nM and the paclitaxel IC_{50} was found to range from 2.5 to 7.5 nM (Abstract; Figures 1-6). Increasing the paclitaxel concentration to 50 nM, however, resulted in no additional cytotoxicity after a 24 hour drug exposure. Prolonging exposure of cells to paclitaxel from 24 hours to 72 hours increased cytotoxicity from 5 to 200 fold in different cell

[1] 1-20% of a conventional dose of paclitaxel of 135-175 mg/m^2 over a period of three weeks is equal to a range of

lines (*id*.). The authors suggest that paclitaxel will be most effective clinically when there is prolonged exposure of tumor to the drug and further that it appears that modest concentrations (*i.e*., 50 nM) should be as effective as higher concentrations of paclitaxel.

Liebmann *et al*. teach that achieving peak tumor drug levels above 50 nM paclitaxel is unlikely to be rewarded with increased tumor response, thus suggesting and motivating one skilled in the art to maintain plasma levels of paclitaxel at less than 50 nM as recited in the instant claims (page 1107, left column). The authors further teach that extended exposure to paclitaxel is likely to result in a greater tumor response than would be expected from the administration of bolus doses of the drug, thus motivating one skilled in the art to administer paclitaxel at low doses over an extended period of time rather than administration of a large bolus dose of paclitaxel (*id*.).

The instantly claimed methods of administering paclitaxel would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made because Broder et al. teach that low but long-term exposure of tumor cells to chemotherapeutic drugs result in better clinical results and minimizes toxicities and and Liebmann et al. suggest that long-term administration of low doses of paclitaxel so as to maintain tumor levels of paclitaxel below 50 nM is likely to be more clinically effective than a single administration of a large bolus dose. In this regard, Broder et al. suggest that maintaining a "window" of stable, steady-state levels of paclitaxel at or close to the ideal range for long periods of time. Because it was known in the art that a 0.05 μM plasma level of paclitaxel would be sufficient to at least inhibit of protein isoprenylation and 2 to 20 nM of paclitaxel are sufficient to be cytotoxic to numerous human tumor cell lines, the skilled artisan would have been motivated to maintain such a plasma level for as long as possible. In accordance with the disclosure of Broder et al., paclitaxel could be administered at a dose and schedule such that a 0.05 μM plasma level of paclitaxel is maintained over an extended period of time, thus keeping the levels within a safe and effective “window” and meeting the limitations of the instant claims (page 26, lines 8-11).

1.35-35 mg/m^2 over three weeks.

Claims 75-78, 80-81, 88-95, 97-98, 106-108, 110-114, 116-117, 125-127, and 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Fennelly *et al***. (Reference A16 on IDS filed 5/12/2003) and **Liebmann *et al***. (Br. J. Cancer, 1993, vol. 68, pages 1104-1109) in view of **Hardman *et al*., eds**. (Goodman & Gilman's The Pharmacological Basis of Therapeutics, 1996, 9th Edition, McGraw-Hill: New York, NY, pages 24-26).

Fennelly *et al*. teach administration of paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 to ovarian cancer patients (Abstract). Paclitaxel was administered *via* a 1-hour infusion thus teaching the instantly claimed "systemically" and "intravenously" as recited in claims 78, 80, 95, 97, 114, and 116 (*id*.). The infusions were administered "weekly" for an average of 10 weeks thus meeting the limitations of claims 91-92, 107-108, 112, and 126-127 (*id*.). Fennelly suggest that the efficacy of paclitaxel may depend on the time that paclitaxel plasma concentration exceeds some critical level (page 187, paragraph bridging left and right columns)

Fennelly *et al*. do not disclose administration of paclitaxel wherein the plasma level of paclitaxel in the subject is maintained at 0.01-0.05 μg/mL over a period of 7 days or more (claim 75) or an amount of paclitaxel that is 1% to 20% of a conventional dose of paclitaxel of 135-175 mg/m^2 over a period of three weeks (claim 90).

However, Liebmann *et al*. disclose that in human tumor cell lines exposed to paclitaxel *in vitro*, the fraction of surviving cells fell sharply after exposure for 24 hours to paclitaxel concentrations ranging from **2 to 20 nM** and the paclitaxel IC_{50} was found to range from 2.5 to 7.5 nM (Abstract; Figures 1-6). Increasing the paclitaxel concentration to 50 nM, however, resulted in no additional cytotoxicity after a 24 hour drug exposure. Prolonging exposure of cells to paclitaxel from 24 hours to 72 hours increased cytotoxicity from 5 to 200 fold in different cell lines (*id*.). The authors suggest that paclitaxel will be most effective clinically when there is prolonged exposure of tumor to the drug and further that it appears that modest concentrations (*i.e*., 50 nM) should be as effective as higher concentrations of paclitaxel.

Liebmann *et al*. teach that achieving peak tumor drug levels above 50 nM paclitaxel is unlikely to be rewarded with increased tumor response, thus suggesting and motivating one skilled in the art to maintain plasma levels of paclitaxel at less than 50 nM as recited in the instant claims (page 1107, left column). The authors further teach that extended exposure to paclitaxel is likely to result in a greater tumor response than would be expected from the

administration of bolus doses of the drug, thus motivating one skilled in the art to administer paclitaxel at low doses over an extended period of time rather than administration of a large bolus dose of paclitaxel (*id*.).

While the primary and secondary references do not explicitly disclose amounts of paclitaxel to achieve the claimed steady-state plasma levels of paclitaxel, Hardman *et al*. teach that in most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion in order to maintain steady-state concentrations of drug in plasma within a given therapeutic range (page 24, right column). In order to maintain the chose steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss (*id*.). Thus, the skilled artisan has the means to administer paclitaxel in a dose and rate of administration so as to achieve the drug target levels suggested and motivated by Liebmann *et al*. (*i.e*., less than 50 nM).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to adjust the administration regimen taught in Fennelly *et al*. such that the plasma level of paclitaxel does not rise above 50 nM because Liebmann *et al*. teach that paclitaxel is cytotoxic to human tumor cell lines at concentrations ranging from 2 to 20 nM and no additional cytotoxic effect when doses are above 50 nM. While Fennelly *et al*. and Liebermann *et al*. do not disclose doses of paclitaxel to achieve a target level of 2 to 20 nM in a subject, Hardman *et al*. teach that the skilled artisan can calculate appropriate rates of drug administration so as to maintain steady-state concentrations of drug in plasma. Thus, the skilled artisan has the means and motivation to administer paclitaxel over extended periods of time in low amounts such that a steady-state concentration cytotoxic to tumor cells is achieved *in vivo*.

Claims 82, 84, 99, 101, 118, and 120 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Fennelly *et al***. and **Liebmann *et al***. in view of **Hardman *et al*., eds**. as applied to claims 75-78, 80-81, 88-95, 97-98, 106-108, 110-114, 116-117, 125-127, and 129 above, and further in view of **WO 98/14174** (Published April 9, 1998) (Reference 46 on IDS filed 9/4/2007).

Instant claims 82, 84, 99, 101, 118, and 120 recite administration of paclitaxel in a slow release delivery vehicle and/or a colloidal dispersion system comprising nanocapsules.

Fennely *et al*., Liebmann et al., and Hardman et al. teach as discussed *supra*. The references do not teach the administration of paclitaxel in a colloidal dispersion system comprising nanocapsules or a slow release delivery vehicle.

However, WO '174 teaches compositions and methods for the *in vivo* delivery of substantially insoluble pharmacologically active agents (such as paclitaxel) in which the active agent is delivered in the form of suspended particles coated with a protein (Abstract). The particulate system of the invention can be converted into a redispersible dry powder comprising **nanoparticles** of water-insoluble drug coated with a protein, and free protein to which molecules of the active agent are bound (*id*.). Invention colloidal systems may be prepared without the use of conventional surfactants and in a preferred embodiment, the invention methods is used to prepare extremely small particles which can be sterile-filtered (page 1, lines 13-18). The nanoparticles of the invention provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection, thus meeting the limitation "slow release delivery vehicles" as recited in the instant claims (page 2, lines 14-16).

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to administer paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also motivates and suggests administering paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Slow release delivery vehicles and colloidal dispersion systems such as nanoparticles are routinely used to deliver pharmacologically active agents. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an administration regimen for paclitaxel that would be clinically

effective and at the same time non-toxic. One skilled in the art is faced with a finite number of predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle or in nanoparticles and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Claims 82-87, 99, 101-102, 104 and 118-123 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Fennelly *et al***. and **Liebmann *et al***. in view of **Hardman *et al*., eds**. as applied to claims 75-78, 80-81, 88-95, 97-98, 106-108, 110-114, 116-117, 125-127, and 129 above, and further in view of **U.S. Patent No. 6,211,171** (Issued Apr. 3, 2001; Filed May 19, 1998).

Instant claims 82-87, 99, 101-102, 104 and 118-123 recite administration of paclitaxel in a slow release delivery vehicle, a colloidal dispersion system, in a polymer of stabilized crystals and in colloidal dispersion systems comprising nanocapsules, microspheres, liposomes, or oil-in-water emulsions.

Fennely *et al*. teach as discussed *supra*. The reference does not teach the administration of paclitaxel in a slow release delivery vehicle, in a polymer of stabilized crystals or in colloidal dispersion systems comprising nanocapsules or microspheres

However, U.S. '171 teaches methods for the *in vivo* delivery of antidepressants (Abstract). At column 11, lines 1-17, compositions formulated for local injections are taught which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals. Colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions,

micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome or microsphere. Liposomes are artificial membrane vesicles which are useful as slow release delivery vehicles when injected or implanted, or when contained within a topical preparation.

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to formulate paclitaxel in a composition suitable for local injection, such as those compositions taught in U.S. '171.

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also teaches compositions suitable for local injection of active agents comprising a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals.

The prior art does not explicitly teach administering paclitaxel in a colloidal dispersion system or in polymer-stabilized crystals using the administration regimen instantly claimed.

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Compositions formulated for local injections, which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals were known in the art. Such colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes as instantly claimed. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an administration regimen for paclitaxel that would be clinically effective and at the same time non-toxic. One skilled in the art is faced with a finite number of predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of

infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals, and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 11/644,850

Claims 75-104, 106-123, and 125-129 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/644,850. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the claimed methods of the 11/644/850 patent fully encompass the instantly claimed subject matter and are generic to the claimed methods of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614